Thrombocytosis and Infections in Childhood

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n both children and adults, thrombocytosis is usually defined as a platelet count of more than 450 × 10^9/μL. As there are many primary and secondary causes, as well as false or “spurious” conditions mimicking thrombocytosis, establishing the cause requires considering clinical features and hematologic parameters. Pediatric primary thrombocytosis is very rare, but reactive thrombocytosis (RT) can be frequently observed in children with infections, iron deficiency, tissue damage, hemolysis, autoimmune diseases, malignancies, and other causes of an acute-phase response. The incidence of secondary forms due to infections is significantly higher in childhood than in adulthood, and infections are the main cause of pediatric RT, with reported incidence rates ranging from 37% to 78%. This wide range may be explained by the cutoff platelet count, the study population (in-patients, out-patients, or both), and the median age of the enrolled subjects.

ETIOPATHOGENESIS

In pediatric patients with infections, RT is due to increased megakaryopoiesis and thrombopoiesis, which can be stimulated up to 10-fold. Under these conditions, platelet production is altered and may be regulated by various cytokines, such as interleukin (IL)-1 alpha, IL-8, IL-6, and tumor necrosis factor. IL-6 plays a major direct and indirect role by stimulating megakaryopoiesis or hepatic thrombopoietin (TPO) production. In the first week of stimulation, when the platelet count is still normal, circulating TPO concentrations peak on day 4 ± 2 days and then gradually decrease. In the second or third week, when platelet counts peak, TPO concentrations are back in the normal range. Furthermore, TPO concentrations usually correlate with those of C-reactive protein and IL-6 levels. This explains why platelet counts in children with RT due to infections mainly peak in the second week and return to normal values within a median of 3 to 4 weeks and always within 3 months.

The platelets are generally small with a normal mean platelet volume. A bone marrow aspirate is not usually required for RT; however, if one is performed because of diagnostic uncertainty, it shows megakaryocytic hyperplasia and a normal mature and left-shifted megakaryocyte morphology. The megakaryocytes have a normal interstitial distribution without clustering, and reticulin levels are typically not increased.

Many reports indicate that bacterial infections are more frequently associated with childhood RT than viral infections. Respiratory tract infections are the most common, followed by gastrointestinal and urinary tract infections; however, RT may also be encountered in children with meningitis, tuberculosis, and human immunodeficiency virus infection. RT is a frequent finding in children with lower respiratory tract infections, especially in the presence of pleural effusions or empyema. It has recently been reported that Mycoplasma pneumoniae infections may sometimes appear with RT as a hematological manifestation, although this infection has mainly been associated with thrombocytopenia. Table 1 summarizes the findings of some of the main pediatric studies of RT during infections.

There is no agreement as to whether platelet counts are prognostic of the outcome of pediatric infections, although a recent study has found that thrombotic patients with lower respiratory tract infections have a more severe clinical evolution than patients without RT, which suggests that increased platelet counts in the second week of illness may be a marker of the severity of pediatric lower respiratory tract infections. The findings of a study of the clinical significance of RT in children with urinary tract infections were similar, and the authors suggested that a high platelet count may indicate the site and severity of infection (upper rather than lower urinary tract infection) and the type of organism (Gram positive rather than Gram negative). In addition, to acute-phase blood markers and renal imaging, platelet counts may be both diagnostically and prognostically useful in the management of pediatric urinary infections.

The authors have no funding or conflicts of interest to disclose.

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The authors have no funding or conflicts of interest to disclose.

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TABLE 1. Characteristics of RT Caused by Infections in Children

<table>
<thead>
<tr>
<th>No. enrolled children</th>
<th>Age range (median age)</th>
<th>No. patients with infections (%)</th>
<th>Type of infection, number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al3</td>
<td>No. not available</td>
<td>900</td>
<td>L</td>
</tr>
<tr>
<td>Vora et al4</td>
<td>25 (27%)</td>
<td>1501</td>
<td>L</td>
</tr>
<tr>
<td>O’Shea et al6</td>
<td>1 2y(9mo)</td>
<td>1 000</td>
<td>L</td>
</tr>
<tr>
<td>Denton et al8</td>
<td>25 (77%)</td>
<td>1 060</td>
<td>L</td>
</tr>
<tr>
<td>Kilpi et al10</td>
<td>57 (74%)</td>
<td>1 100</td>
<td>L</td>
</tr>
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</table>

Table 1 continued...
of 311 children with bacterial meningitis after the first week of treatment, and that it had no influence on the neurologic outcome of the surviving patients, thus demonstrating that the patients who died developed thrombocytopenia rather than RT.13

Moreover, some studies have shown that RT can also occur during antibiotic treatment for pediatric infections. It may appear as a laboratory side effect after treatment with carbapenems (ie, imipenem/cilastatin, meropenem) and cephalosporins (ie, ceftriaxone and ceftazidime) in the case of neonatal and childhood central nervous system or respiratory tract infection, and it has an incidence of nearly 10% in treated patients.14 It has also been reported that there is an association between RT and the use of antifungal therapy for childhood candidemia.15

The occurrence of childhood RT is age dependent: the highest incidence is found among neonates (particularly preterm babies) and infants aged up to 24 months, which gradually decreases up to the age of 10 years. Mastubara et al studied 456 Japanese thrombocytotic children, more than 80% of whom were aged less than 2 years and only 3% were aged 8 to 10 years.9 Similar results have been reported by O’Shea et al, who found that the majority of European children with RT due to infections are less than 2 years old.9

TREATMENT

As thromboembolic events have not been reported in children with RT secondary to infections, treatment with platelet aggregation inhibitors is not required even when the platelet count is high (ie, >1000 × 109/L).10 It is important to remember that a conservative approach is recommended and treatment should be aimed at the underlying infection and not the platelet count.

REFERENCES